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(54) Title: FORMULATIONS AND METHODS FOR REDUCING SKIN IRRITATION

(57) Abstract

Compositions and formulations containing multiply-protonated organic polyamines (such as amino acids with amine-containing side groups), and methods of using the same, for inhibiting skin irritation in animals.

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FORMULATIONS AND METHODS FOR REDUCING SKIN IRRITATION

Related Applications

This application is a continuation-in-part of U.S. Patent Application Serial No. 08/384,263, filed February 3, 1995 by the present inventors, the entire contents of which are incorporated herein by reference.

Background

Many substances are applied topically to the skin or mucous membranes of humans or animals (hereafter "skin") in order to alter the subject's appearance, to protect the subject from the environment, or to produce a biological change in the skin or other tissue for therapeutic, preventive or cosmetic purposes. These substances may generically be termed "topical products" and include such substances as cosmetics, over-the-counter and prescription topical drugs, and a variety of other products such as soaps and detergents.

Topical products occur in a variety of forms, including solids, liquids, suspensions, semisolids (such as creams, gels, pastes or "sticks"), powders or finely dispersed liquids such as sprays or mists. Examples of topical products commonly classified as "cosmetics" include skin care products such as creams, lotions, moisturizers and "treatment cosmetics" such as exfoliants and/or skin cell renewal agents; fragrances such as perfumes and colognes, and deodorants; shaving-related products such as creams, "bracers" and aftershaves; depilatories and other hair removal products; skin cleansers, toners and astringents; pre-moistened wipes and washcloths; tanning lotions and sunscreens; bath products such as oils; eye care products such as eye lotions and makeup removers; foot care products such as powders and sprays; skin colorant and make-up products such as foundations, blushes, rouges, eye shadows and liners, lip colors and mascaras; lip balms and sticks; hair care and treatment products such as

shampoos, conditioners, colorants, dyes, bleaches, straighteners, and permanent wave products; baby products such as baby lotions, oils, shampoos, powders and wet wipes; feminine hygiene products such as deodorants and douches; skin or facial peels applied by dermatologists or cosmeticians; and others. Examples of topical products commonly classified as "topical drugs" are many and varied, and include over-the-counter and/or prescription products such as antiperspirants, insect repellents, ocular drugs and eye care products, both therapeutic and non-therapeutic, including eyedrops, rewetting drops, saline solutions and contact lens solutions, sunscreens and sunburn treatments, anti-acne agents, antibiotics, topical respiratory agents, therapeutic retinoids, anti-dandruff agents, external analgesics such as capsaicin products, topical contraceptives, topical drug delivery systems, gastrointestinal agents, suppositories and enemas, hemorrhoid treatments, reproductive tract agents such as vaginal treatments, lozenges, and many other products with therapeutic or other effects, for use on skin or mucous membranes, including ocular, nasal, otic, laryngopharyngeal, and pulmonary membranes. Other topical products include hand, facial and body soaps and detergents and other forms of skin cleansers, as well as household detergents and many other household products such as solvents, propellants, polishes, lubricants, adhesives, waxes and others which are either applied topically or are topically exposed to the body during normal use.

In a large number of cases, topical products contain chemicals which may produce "irritation," including various inflammation symptoms, when applied to the skin or mucosa ("skin"). The present invention is directed in part to compositions and methods for inhibiting the irritation associated with such topical products.

The occurrence, frequency and nature of topical-product-induced irritation often varies from user to user. The severity of irritation to the susceptible user may range from subclinical to mild to severe. Typical symptoms of "irritation"

include itching (pruritus), stinging, burning, tingling, "tightness," erythema (redness) or edema (swelling). The irritation response may be due to the direct effect on the skin of certain topical product chemicals or to a response by the immune system directed toward the chemicals alone or in combination with skin components (e.g. allergic dermatitis).

The sensation of itch is one of the most common skin problems experienced by humans and animals. Itch can be defined as a sensation which provokes the desire to scratch the site from which the sensation originates. All skin contains sensory nerves which can transmit itch or other similar sensory impulses in response to chemical irritation, environmental exposure or disease processes. Although the precise population of itch-producing nerves have not been identified, the thinnest unmyelinated nerve population, termed type C nociceptive neurons are thought to be the most important in producing the sensation. Itch: Mechanisms and Management of Pruritus. Jeffrey D. Bernhard, ed. (McGraw-Hill, Inc., San Francisco, 1994), pp. 1-22. The itch-producing nerves of the skin can be considered to be a "final common pathway" for the many irritating conditions which are ultimately sensed as itch, including chemical exposure, environmental exposure (such as that which produces dry, itchy skin) and disease processes such as atopic dermatitis. Many chemical substances are able to produce itch when topically applied to the skin. No matter what the ultimate cause of itch, the sensation experienced is the same and provokes the desire to scratch.

Many ingredients used in topical products are known irritants or are potentially irritating, especially to people with "sensitive skin". These irritating ingredients include fragrances, preservatives, solvents, propellants and many other ingredients that might otherwise be considered inert components of the products. Additionally, many topical product active ingredients, including chemicals that may also be classified as drugs, produce irritation when applied

to the skin or mucous membranes. These include, but are not limited to, such ingredients as exfoliants and skin cell renewal agents, anti-acne drugs, antiperspirant compounds, antihistamines, anti-inflammatory agents, skin protective agents, insect repellent chemicals, sunscreens, nasal and respiratory medications in the form of mists or sprays, and many others. Where more than one chemical irritant is present, their irritating effects may be additive. Furthermore, chemical ingredients may react with one another, or in the environment of the skin, to form new chemicals which are irritating. The vehicles in which the active drug ingredients are formulated may also produce irritation in sensitive people, especially in the case of drugs such as topical corticosteroids.

In addition to chemicals which directly trigger skin irritation, some chemicals indirectly cause the skin to become more sensitive to other chemicals or environmental conditions which would not normally cause irritation. Many chemicals which act as skin "exfoliants" such as retinoids (e.g. tretinoin, retinol and retinal), carboxylic acids including α-hydroxy acids (e.g. lactic acid, glycolic acid), β-hydroxy acids (e.g. salicylic acid), α-keto acids, acetic acid and trichloroacetic acid, l-pyrrolidone-5-carboxylic acid, capryloyl salicylic acid, α-hydroxy decanoic acid, α-hydroxy octanoic acid, gluconolactone, methoxypropyl gluconamide, oxalic acid, malic acid, tartaric acid, mandelic acid, benzylic acid, gluconic acid, benzoyl peroxide and phenol, among others, may cause the skin to become more sensitive to irritation triggered by other topically-applied chemicals such as moisturizers, sunscreens, fragrances, preservatives, surfactants (e.g. soaps, shaving cream) and other topical products. Exfoliants and other ingredients may also increase the skin's sensitivity to environmental conditions such as sunlight, wind, cold temperature and dry air, or to chemical agents such as allergens, or may exacerbate the irritation attributable to a pre-existing skin disease.

Conversely, environmental influences may themselves increase the skin's sensitivity to chemicals in topical products by reducing the epidermal skin's "barrier function." The barrier function acts to minimize absorption or passage of potentially irritating chemicals through the outer "dead" cell layer of epidermal skin into the living skin tissue. Extremes of humidity, for example, can greatly increase irritation from topically-applied products. A very common condition due to low humidity is termed "winter itch" in which the very low humidity characteristics of many cold climates (particularly when accompanied by indoor heating) or long exposure to refrigerated air from air conditioners in the summer produces itchy skin -- especially in older people -- which can exacerbate the irritating effects of topical products. Additionally, soaps, detergents, cleansing products, shaving creams, alcohol and other products which remove some of the skin's protective lipids and/or secretions may increase the skin's permeability and sensitivity to topically-applied chemicals which would otherwise not produce irritation. Normal processes such as sweating may also increase the ability of irritant materials, such as antiperspirants, deodorants or sunscreens, to penetrate the skin through pores or glands, thus exacerbating the potential for irritation. Exposure of the skin to high humidity environments or liquids may also increase the ability of potential irritants to penetrate the skin. Similarly, the skin may become sensitized or inflamed due to infection, shaving abrasion, repeated or excessive washing or bathing, sun exposure, or other mechanical abrasion or injury, resulting in sensory irritation responses upon subsequent application of underarm deodorants, after-shaves or other topical products.

In addition to chemical and environmental causes of skin irritation, many people have an inherent sensitivity or genetic predisposition to skin irritants. People with respiratory allergies, for example, tend to have excessively dry skin which facilitates increased absorption of potentially irritating chemicals. The

excessively dry skin which accompanies atopic dermatitis, for example, predisposes patients with this condition to irritation from many topically-applied products. Other skin diseases and conditions such as allergic or non-allergic contact dermatitis, asthma (including exercise-induced asthma as may be precipitated by inhalation of cold or dry air), hay fever, allergic rhinitis, inflammatory bowel disease, psoriasis, eczema, candidiasis, post-herpetic neuralgia, infectious diseases manifested by, for example, sore throat or skin lesions, insect bites and the like produce inherent irritation which may be exacerbated by application of topical products or by exposure to chemical or environmental influences such as allergens, cold air, low humidity and the like. Many other individuals exhibit sensitive skin as a condition that is not related to an identifiable skin disease.

Whatever the exact cause of irritation, many attempts have been made to reduce the irritation potential of topical products by identifying chemicals which tend to cause irritation and reducing their concentration or eliminating them from the products. Many of these products are advertised to consumers as "hypoallergenic" or the like to designate a product's reduced tendency to cause irritation in consumers with sensitive skin. Most skin (including mucosal) irritation responses, however, are not allergic in origin. In any event, it is often not feasible or practical to identify or eliminate all of the irritating chemical(s), particularly when the irritating chemical(s) are the active ingredient(s) of the product or are required for formulation, preservation or other functional reasons.

As one example, there is a substantial practical and commercial need in the field of exfoliants and related skin care products for a composition or method that will reduce or prevent the irritation caused by such products. Common exfoliants include α- and β-hydroxy carboxylic acids such as lactic acid, glycolic acid, salicylic acid and the like, α-keto acids such as pyruvic acid, as well as assorted compounds such as acetic acid and trichloroacetic acid, l-pyrrolidone-5-

carboxylic acid, capryloyl salicylic acid, α-hydroxy decanoic acid, α-hydroxy octanoic acid, gluconolactone, methoxypropyl gluconamide, oxalic acid, malic acid, tartaric acid, mandelic acid, benzylic acid, gluconic acid, peroxides, phenols, and skin cell renewal agents such as retinoids. Such products are used as exfoliants and/or cell renewal agents to reduce the occurrence or severity of skin wrinkles, particularly facial wrinkles, or as anti-acne, anti-"dry skin" or skin whitening agents. See U.S. Patent Nos. 4,105,782, 4,105,783, 4,246,261, and 5,091,171 (Yu et al.) and 5,262,153 (Mishima et al.); W.P. Smith, "Hydroxy Acids and Skin Aging," Soap/Cosmetics/Chemical Specialties for September 1993, p. 54 (1993). Hydroxy acids, in concentrations high enough to exfoliate, are well known often to cause skin irritation and rashes. The danger of irritation is even higher for persons that have sensitive skin.

Currently available methods reported by Yu et al. to reduce the irritation caused by hydroxy- and keto-acids in topical products include adding a strong alkali metal base such as sodium hydroxide or potassium hydroxide, thereby raising the pH of the preparation and reducing the acidity of the hydroxy acid. Such methods have the reported drawback of reducing the ability of the resulting hydroxy acid salt to penetrate the skin and thus compromising the beneficial effects (particularly anti-acne or anti-"dry skin" effects) of the hydroxy acid. Alternatively, Yu et al. have proposed the approach of reacting the hydroxy acid with a non-alkali metal base such as ammonium hydroxide or an organic base such as a primary, secondary or tertiary organic amine, thereby forming an amide or ammonium salt of the active ingredient hydroxy (or keto) acid. See U.S. Patent Nos. 4,105,782 and 4,105,783 (Yu et al.). The effect of such formulations is, again, to raise the pH of the preparation to a non-irritating level. However, the increased pH (reduced acidity) of the resulting preparations renders them less efficacious as exfoliating or anti-wrinkle agents, which desirably have an acidity equivalent to pH 1-6, and more preferably pH 2-4. See Smith, above, at Table

1. Other approaches to reducing the irritation associated with exfoliant products include the use of slow-release topical formulations such as polymer-based vehicles (see, e.g., Chess et al., U.S. Patent No. 4,971,800) or microsponges, and inclusion of, e.g., plant-derived anti-irritant components (see, e.g., Smith et al., U.S. Patent No. 5,028,428).

A clear need exists, therefore, for a composition or method that prevents or reduces the skin irritation caused by low-pH (high-acidity) organic or inorganic acid products but that does not reduce the efficacy of the acids as exfoliant/cell-renewal agents. More generally, it would be highly desirable to identify compounds with anti-irritant activities that would reduce the irritation caused by a wide range of otherwise safe and effective topical products, or to reduce the intrinsic irritation associated with various skin diseases and conditions (such as atopic dermatitis, allergic dermatitis, asthma (including exercise-induced asthma), hay fever, allergic rhinitis, inflammatory bowel disease, or other respiratory allergy, eczema or psoriasis) or caused by exposure to irritating chemicals or environmental conditions such as allergens, sun, wind, cold air or extremes in humidity.

As explained in more detail below in the Detailed Description, the present invention involves the surprising discovery that multiply-protonated organic polyamines (i.e., organic molecules containing two or more protonated amino functional groups), are effective in reducing the incidence and severity of irritation associated with topically applied skin irritants. In these polyamine anti-irritant compounds, a plurality (two or more) of the amino moities (which may be primary, secondary, tertiary, or quarternary amino functions) are protonated at the particular pH of the topically applied composition or product. It is particularly preferred that the mutiply-protonated polyamines of the present invention are amino acids containing a positively-charged nitrogen-containing side chain, and derivatives of these amino acids.

Amino acids are the chemical units from which proteins are made. "Amino acids" as a class are chemically based upon the so-called "natural" 20 amino acids, which are found in nature. They all have a primary amino function ($-NH_2$) and a carboxylic acid function (-COOH) which are joined to the same carbon atom (-α-amino acids) or to neighboring carbons (e.g., β-amino acids). Similar structures in this class include alpha-imino acids (e.g., proline). In addition, analogs and homologs of the natural amino acids (commonly referred to as "unnatural" amino acids, isomers and enantiomers) may also be synthesized. Amino acids and their analogs and homologs may be chemically modified to prepare unique amino acid structures. These modifications include those in which a chemical modification or substitution on the amino, carboxyl or side chain structures (derivatives) alters the amino acid.

The exact mechanism (or mechanisms) of activity of such polyamines is not known and the invention is not limited to any particular mechanism. However, it is presently believed that it is the presence of positive charge(s) on the compounds of the present invention, especially where the compounds possess multiple sites of protonation, which contributes to the anti-irritant properties of these polyamines. Surprisingly, the inventors have discovered that the anti-irritant activity of the compounds of the present invention is maintained even where the polyamine compound possesses, in addition to multiple centers of protonation, a negatively-charged functional group (e.g., HEPES, N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid], a common biological buffer which contains, at pH's between about 1 and 7, two protonated amino moieties and one negatively-charged sulfonate functional group). In a related context, applicants have discovered that various metal cations are effective at reducing irritation caused by topical application of skin irritants. In this regard, reference is made to the anti-irritant agents disclosed in Patent Application Serial Nos. 08/362,100, 08/362,101, 08/362,097, 08/362,055 and 08/362,058 (entitled

"Formulations and Methods for Reducing Skin Irritation"), filed on December 21, 1994 by the present inventors, the contents of which are incorporated by reference in their entirety.

While applicants do not wish to be bound to any particular mechanism, it is presently proposed that the positive charge(s) on these anti-irritant compounds (e.g., the amino acids of the present invention may have either one or two protonated (and positively-charged) sites, depending on the particular pH typically used in topical products) may reduce irritation by interacting with epidermal or mucosal nerve cells to prevent or counteract the sensation of irritation, and/or by interfering with irritation-inducing components of skin cells that are triggered by the application of the skin irritant. Thus, the positive charge(s) may alter the ability of skin nerve cells to depolarize or repolarize, as for example, by blocking or interfering with ion channel or pump operation or by altering the transmembranal action potential, or the positive charge(s) may interfere with the transmission of nerve impulses from one nerve cell to another. The positive charge(s) on the protonated polyamines may non-specifically bind to cell membranes and contribute to a charge shielding effect, which consequently, alters the ion regulatory activity of the cells.

Amines, particularly amino acids, are widely found in a variety of commercial topical products, especially cosmetics such as skin creams or emollients and hair care products. Small amounts of amino acids are added to these products because of their humectant properties, as they are believed to enhance transdermal penetration of water and other compounds. A Consumer's Dictionary of Cosmetic Ingredients, 3rd edition, Ruth A. Winter, ed. (Crown Publishers, New York, 1989), p. 33; U.S. Patent No. 4,732,892 (Sarpotdar et al.). In addition, specific forms of some amino acids have been used in topical skin preparations for a variety of applications. For example, salts of glutamic acid, an amino acid containing an acidic negatively-charged side chain, have

been found to be useful as topical agents in relieving the discomfort associated with insect bites. See U.S. Patent No. 4,062,937 (Rea). Sodium dihydroxyethylglycine has been used in formulating cleansing and disinfecting solutions which are also claimed to reduce pain and itching. See U.S. Patent No. 4,868,213 (Farrish). Additionally, N-acylates of amino acids and their salts, formed by butyric acid, have been used to treat wrinkles of the human skin. See U.S. Patent No. 4,859,653 (Morelle et al.).

The human skin presents a complex sensory and structural environment. For example, the skin contains nerves and highly specific sensory organs that are specialized and disposed so as to differentiate the stimuli leading to such distinct sensations as heat, cold, pressure, pain, itch and the like. In addition to normal sensory stimuli, nerves in the skin are also responsive to native or foreign chemicals such as proteases, prostaglandins, complement-system molecules, allergens, mitogens and the like which may be presented due to tissue injury or environmental exposure. Agents which are effective to combat one source of sensory stimulus -- for example, steroidal agents to treat skin inflammation -- are ineffective against other sensory stimuli such as pressure, heat, or the transitory sting or itch caused by an applied skin care product. Conversely, local anesthetic agents which are effective to depress all sensory or even motor activity in a treated region are not desirable if only a single sensation -- for example, a transitory sting or itch -- is sought to be eliminated. To complicate the situation, the structural matrix of the epidermal skin affords a "barrier function" which tends to exclude or inhibit the entry of foreign material, including potentially therapeutic agents.

Accordingly, it would be desirable to identify agents which are effective in the skin to inhibit certain identified sensory responses (as, for example, pain or itch) while not adversely affecting other nervous responses in the same tissue (as, for example, tactual sensations). The present invention provides

compositions and methods for reducing specific irritant effects from a variety of sources without negative effects such as caused by the use of anesthetics.

All publications, patents and other reference materials referred to in the present specification are incorporated herein by reference.

Summary of the Invention

The present invention is directed to the use of multiply-protonated organic polyamines (organic molecules containing two or more protonated amino functions), preferably, amino acids (and their derivatives) that possess a positively charged nitrogen-containing side chain, as ingredients to provide fast-acting, efficient and safe topical skin anti-irritant effects, and to formulations containing such compounds. It is one object of the present invention to provide ingredients, formulations and methods of use which can suppress skin irritation due to chemical or environmental exposure, or due to tissue inflammation, injury or other skin pathology. The invention is particularly useful for preventing, reducing or eliminating the potential irritation caused by topical application of products containing other irritating ingredients, including cosmetics such as, especially, hydroxy acid or other exfoliant containing products, facial peels, shaving products, sunscreen products, deodorants and other cosmetics as described above, as well as topical drug products containing irritating active ingredients or vehicles, and other products such as soaps, detergents, solvents and the like which are either applied topically or are topically exposed to the body during use. Thus, the present invention meets a clear need for formulations and ingredients that will prevent or reduce the potential skin irritation caused by topical products. The invention is also useful for preventing, reducing or eliminating the skin irritation caused by skin diseases or other conditions such as environmental exposure to irritating chemicals or influences such as wind, heat, cold and extremes in humidity, including the intrinsic irritation associated

with these conditions as well as such irritation as may be exacerbated by the application of a topical product.

In a preferred embodiment, the polyamine anti-irritants of the invention are included in a suitable topical vehicle at a concentration of about 10 to about 3000 mM, more preferably about 50 to about 2000 mM, and most preferably about 100 to about 1000 mM.

In another preferred embodiment, one or more of the polyamines of the invention are combined in a topical product formulation further comprising a potentially irritating ingredient, the polyamine(s) being present in a total amount effective to reduce or eliminate irritation due to the irritant ingredient. In one particularly preferred embodiment, a polyamine anti-irritant component of the present invention is combined in a hydroxy acid or other exfoliant preparation such that the pH of the hydroxy acid preparation is maintained in the range of pH 1-6, and more preferably, in the range of pH 2-4. It will be understood that, where the formulation employs an anhydrous vehicle, the acidity of the formulation may not be expressible in typical pH terms, but that such acidity will manifest itself upon exposure of the formulation to the skin where water is present both intracellularly and extracellularly.

In another embodiment, the compounds of the present invention may be combined in a formulation with other anti-irritants, such as steroidal or non-steroidal anti-inflammatory agents or other materials such as aloe vera, chamomile, α-bisabolol, Cola nitida extract, green tea extract, tea tree oil, licorice extract, allantoin, urea, caffeine or other xanthines, glycyrrhizic acid and its derivatives, or with other anti-irritant species such as those identified in co-pending U.S. Patent Application Serial Nos. 08/362,100, 08/362,101, 08/362,097, 08/362,055 and 08/362,058 (entitled "Formulations and Methods for Reducing Skin Irritation"), filed on December 21, 1994 by the present inventors, so as to achieve a multiple anti-irritant effect.

Further, it is presently believed that the irritation-reducing properties of the polyamine anti-irritants of the present invention are additive if fractional portions of different species of polyamines are combined so as to make up a total combined concentration within the ranges referred to above. Therefore, it is contemplated that mixtures or combinations of the claimed amino acid anti-irritants may be used at the appropriate total concentration to be effective at reducing irritant properties, regardless of the concentration of any one anti-irritant component.

The invention further provides methods of treating, reducing or eliminating skin irritation comprising the topical application of a formulation comprising an anti-irritant effective amount of one or more polyamines of the invention. The formulation may further include one or more potentially irritating components. Alternatively, the formulation may be applied separately and prior to application of another product containing a potentially irritating component, or the formulation may be applied alone in order to prevent the development of irritation or to treat a pre-existing irritation attributable to conditions such as skin disease, chemical irritant exposure or environmental exposure.

Detailed Description

Human clinical trials undertaken in connection with the present invention have established that aqueous-soluble multiply-protonated polyamines, including amino acids (and derivatives thereof) having a positively-charged nitrogen-containing side chain, are effective when applied topically to the skin in appropriate concentrations and vehicles to suppress the relatively severe stinging, burning, tingling, itching and/or erythema induced by topical application of the hydroxy acid skin irritant lactic acid. Formulations containing such anti-irritant compounds are useful in suppressing a wide range of topical-product-induced irritation responses

attributable to exfoliants, sunscreens, retinoids, anti-perspirants, deodorants, anti-acne and other products which contain components potentially capable of causing sensory irritation. For example, the compounds of the present invention are useful for preventing or reducing the skin irritation caused by α- or β-hydroxy acids, α-keto acids and other carboxylic acids, as well as retinoids, phenols, peroxides and similar irritants found in over-the-counter topical products for home or cosmetologist use (such as l-pyrrolidone-5-carboxylic acid, capryloyl salicylic acid, α-hydroxy decanoic acid, α-hydroxy octanoic acid, gluconolactone, methoxypropyl gluconamide, oxalic acid, malic acid, tartaric acid, mandelic acid, benzylic acid, and gluconic acid), as well as in certain prescription topical drugs containing high (for example, 12% w/w or even higher) dosage forms of such irritants. The irritation attributable to combinations of such irritating ingredients, such as lactic acid/salicylic acid combinations and hydroxy acid/retinoid combinations, as well as irritation attributable to purified isomeric forms of such ingredients, can also be inhibited by the formulations of the invention. Additionally, formulations containing such compounds are useful in ameliorating irritation in conditions where the skin is inherently hypersensitive to topical products (e.g. dry skin, "winter itch," and other inflammation or injury conditions) and in ameliorating the irritation due to such conditions even in the absence of other applied topical products. The formulations are also useful in treating non-human animal skin irritation, as for example dog or cat irritation and resultant scratching due to fleas or other skin disease or condition.

An additional benefit of the present anti-irritant compounds and formulations is that they do not have the undesirable anesthetic side-effects exhibited by lidocaine and other similar skin local anesthetics. Upon application of a solution of the compound used in the clinical trials described here, subjects typically reported no

sensations other than those sensations caused by the vehicle alone, and no lack of normal sensation(s).

The protonated polyamines of the present invention include straight-chain and branched-chain polyamines, as well as heterocyclic amines. The protonated amino moieties of these polyamine molecules may be primary, secondary, tertiary, or quarternary amino functions. In addition to the amino acid compounds described herein, the polyamine anti-irritant compounds are preferably selected from the group consisting of spermine, spermidine, putrescine, protamine, HEPES, imidazole, and piperazine, since these polyamines possess two or more protonated amino groups under acidic conditions (low pH).

Where the polyamines of the present invention are amino acids, they are preferably selected from the group consisting of arginine, lysine, histidine, and ornithine, since these amino acids have, in addition to a positively-charged N-α amino moiety, a positively-charged side chain amino function at physiological pH and below. Arginine, lysine, histidine, and ornithine possess predominantly two positive charges at low pH (pH <5), one positive charge on the side chain amine group and another positive charge on the N-α terminus of the amino acid backbone. It is believed that the multiply-protonated state of these amino acids at low pH contributes to these compounds' anti-irritant properties.

In addition to the aforementioned amino acids, substituted or otherwise derivatized forms of such amino acids are also within the scope of the present invention. Herein, derivatized amino acids also include analog forms of the amino acids. Preferred substituents include substituents (at either or both of the N-α-terminus and the C-terminus ends of the amino acid) at the N-α-terminus of the amino acid of the form RCO- or R-, carboxyl (C)-terminal substituents of the form $-NH_2$, $-NHNH_2$, and -NHR, where each R is independently an unsubstituted or

substituted alkyl, alkenyl or alkynyl (either unbranched or branched, and preferably from 1 to about 10 carbons), or aryl, alkaryl, aralkyl or cycloalkyl (preferably of from about 3 to 20 carbons), or, in the case of $-NR_2$, the R- groups are together a cyclized group forming (in attachment with the nitrogen atom) a 5-8 membered heterocyclic ring optionally containing an oxygen or nitrogen as a further ring heteroatom.

An amino-terminal acetyl substituent is a particularly preferred substituent for the derivatized amino acid compounds. Amidating or esterifying carboxyl-terminal substituents formed from unsubstituted or lower alkyl-substituted amino, or from lower alkoxy or single-ring aryloxy, groups are preferred, and groups of the form $-NH_2$, $-OCH_3$, $-OCH_2CH_3$ are especially preferred. Amidating substituents are particularly preferred. Where an amidating group of the structure $-NR_2$ is to be cyclic in form, the N-morpholino heterocyclic structure is preferred.

Other suitable substituents are readily available commercially or may be prepared by one skilled in the art and evaluated for anti-irritant activity with routine testing.

Further, it has been found that both D- and L- forms of the amino acid anti-irritant compounds of the present invention exhibit irritant reducing activity. It is expected that guanidinium, a triamine side chain constituent of arginine, may also be effective at reducing irritation. Similarly, other isomeric forms, homologs and suitable salts of the amino acid compounds are predicted to be active.

Formulations of the Invention

The anti-irritant topical formulations of the invention comprise a topical vehicle suitable for administration to the animal (particularly human) skin, and an amount of one or more polyamine anti-irritant compounds of the invention effective

to reduce, inhibit or eliminate existing or potential skin irritation or inflammation. In one embodiment, the anti-irritant topical formulations additionally contain an irritant ingredient(s) that is itself capable of inducing skin irritation, such as symptoms associated with inflammation, as, for example, a cosmetic or skin care product ingredient, or a pharmaceutically active ingredient or drug ingredient.

The polyamine anti-irritant compounds for use in the anti-irritant formulations of the invention are contained in a topical formulation in a concentration effective to prevent or reduce (hereafter, "inhibit") the skin irritation and/or inflammation (such as inflammation) symptoms that are sought to be eliminated. The formulation preferably contains the selected compound in a suitable topical vehicle at a total concentration of about 10 to about 3000 mM, more preferably about 50 to about 2000 mM, and most preferably about 100 to about 1000 mM. The appropriate concentration can be achieved using a single polyamine anti-irritant component of the invention, or multiple different such compounds may be combined to yield the total desired concentration. If other anti-irritant components are included in the formulation, then lower concentrations of the compounds of the invention may be utilized.

Preferred concentrations can also be expressed in weight/volume or weight/weight percentage terms which will vary somewhat depending on the density of the vehicle and other components in the formulation. Thus, to take an example in which the vehicle has a density of 0.93 g/ml (as in a 50:50 [by volume] mixture of 95% ethyl alcohol and water) and the nitrogenous compound is incorporated in the form of histidine (formula weight 155), representative molarity concentration values correspond approximately to

100 mM:	0.78% (w/v)	0.83% (w/w)
500 mM:	3.88% (w/v)	4.17% (w/w)
1000 mM:	7.75% (w/v)	8.33% (w/w)

The preferred concentration ranges expressed above contemplate that a typical topical dosage will be approximately 0.5 grams of formulation over a 5 cm x 5 cm area of skin (25 cm^2). Clinical studies have shown that such preferred concentration ranges are generally effective to inhibit skin irritation. In typical topical vehicles, the compositions are readily formulated and do not leave any significant visible residue when applied to the skin. Higher concentration formulations, such as saturated pastes or other forms, may also be successfully used, particularly where visible appearance is not a limiting consideration (as in therapeutic applications).

Furthermore, routine clinical assessments such as those described below can readily be employed to optimize the concentration of the polyamine anti-irritant compound(s) of the invention and to ascertain if lower, or higher, concentrations are appropriate for a given formulation or irritation indication. For example, the concentration may be adjusted to account for the amount of formulation that is typically applied to a given skin area by the user, which will depend to an extent on the physical nature of the topical vehicle (e.g., lotion as compared to liquid spray vehicles). Likewise, the amount of the compound required may be reduced in such cases where the formulation contains a skin penetration-enhancing ingredient or other agent which increases the ability of the compounds to permeate the stratum corneum to their site of anti-irritant activity. Preferably, the formulations of the invention include an amount of polyamine anti-irritant compound (or compounds) capable of inhibiting irritation in susceptible individuals by at least about 20% or

more, as measured by a mean reduction in cumulative irritation across a susceptible test population as exemplified in the clinical protocols described below. Alternatively, the formulations of the invention include an amount of anti-irritant compound capable of inhibiting irritation by at least about 40% or more in at least about 10% of the susceptible population, as measured by a reduction in cumulative irritation on an individual-by-individual basis (treated vs. control areas). This latter measure of efficacy reflects the fact that the present formulations, similar to many therapeutic products, may in some cases be effective in delivering a significant benefit to some, but not all, of the susceptible population.

The optimum concentration of a compound of the invention may be reduced below (or within) the preferred ranges set forth above if some other anti-irritant component is included in the formulation along with the polyamine anti-irritant compound of the invention. In particular, it is contemplated that lower (e.g. halved) amounts of the anti-irritant species may be used, while still maintaining comparable levels of anti-irritant activity, by further including an approximately equal concentration of, for example, a calcium-channel blocking or regulatory agent, or other anti-irritant agent such as a steroid or non-steroidal anti-inflammatory agent. Examples of suitable additional anti-irritant ingredients are described in applicants' U.S. Patent Application Serial Nos. 08/362,100, 08/362,101, 08/362,097, 08/362,055 and 08/362,058 (entitled "Formulations and Methods for Reducing Skin Irritation"), filed December 21, 1994 and incorporated by reference in their entirety. Other anti-irritant ingredients, such as aloe vera, chamomile, α-bisabolol, Cola nitida extract, green tea extract, tea tree oil, licorice extract, allantoin, urea, caffeine or other xanthines, and glycyrrhizic acid and its derivatives, may also be beneficially incorporated into the formulations of the invention in order further to inhibit irritation effects or symptoms.

The compounds of the invention are typically incorporated into the present formulations by mixing an appropriate amount of a sufficiently soluble form of the selected compound into the chosen formulation vehicle at an appropriate pH such that the polyamine is multiply protonated (e.g., where the side chains of the amino acid compounds are positively charged), along with such other skin care components as are desired. From a formulation standpoint, it is preferred that the selected compound be sufficiently soluble in the formulation vehicle as to allow a consistent formulation having the desired physical and topical application characteristics. It is also highly preferred that the compound (or compounds) chosen be sufficiently aqueous-soluble such that, upon application to the skin, the component compounds are taken up into the water-containing milieu of the skin. In addition, it will be clear that the anti-irritants chosen should be topically acceptable and preferably will not themselves be irritating, toxic or otherwise deleterious to the user.

Suitable topical vehicles for use with the formulations of the invention are well known in the cosmetic and pharmaceutical arts, and include such vehicles (or vehicle components) as water; organic solvents such as alcohols (particularly lower alcohols readily capable of evaporating from the skin such as ethanol), glycols (such as glycerin), aliphatic alcohols (such as lanolin); mixtures of water and organic solvents (such as water and alcohol), and mixtures of organic solvents such as alcohol and glycerin (optionally also with water); lipid-based materials such as fatty acids, acylglycerols (including oils, such as mineral oil, and fats of natural or synthetic origin), phosphoglycerides, sphingolipids and waxes; protein-based materials such as collagen and gelatin; silicone-based materials (both non-volatile and volatile) such as cyclomethicone, demethiconol and dimethicone copolyol (Dow Corning); hydrocarbon-based materials such as petrolatum and squalene; anionic, cationic and amphoteric surfactants and soaps; sustained-release vehicles such as

microsponges and polymer matrices; stabilizing and suspending agents; emulsifying agents; and other vehicles and vehicle components that are suitable for administration to the skin, as well as mixtures of topical vehicle components as identified above or otherwise known to the art. The vehicle may further include components adapted to improve the stability or effectiveness of the applied formulation, such as preservatives, antioxidants, skin penetration enhancers, sustained release materials, and the like. Examples of such vehicles and vehicle components are well known in the art and are described in such reference works as Martindale -- The Extra Pharmacopoeia (Pharmaceutical Press, London 1993) and Martin (ed.), Remington's Pharmaceutical Sciences.

The choice of a suitable vehicle will depend on the particular physical form and mode of delivery that the formulation is to achieve. Examples of suitable forms include liquids (including dissolved forms of the compounds of the invention, as well as suspensions, emulsions and the like); solids and semisolids such as gels, foams, pastes, creams, ointments, "sticks" (as in lipsticks or underarm deodorant sticks), powders and the like; formulations containing liposomes or other delivery vesicles; rectal or vaginal suppositories, creams, foams, gels, ointments, enemas, douches and other forms. Typical modes of delivery include application using the fingers; application using a physical applicator such as a cloth, tissue, swab, stick or brush (as achieved, for example, by soaking the applicator with the formulation just prior to application, or by applying or adhering a prepared applicator already containing the formulation -- such as a treated or premoistened bandage, wipe, washcloth or stick -- to the skin); spraying (including mist, aerosol or foam spraying, such as nasal sprays); dropper application (as, for example, with ear or eye drops); sprinkling (as with a suitable powder form of the formulation); soaking; and injection (particularly intradermal or subcutaneous injection). Iontophoresis or other

electromagnetic-enhanced delivery systems may also be usefully employed, as for example to increase delivery to the dermis.

Methodologies and materials for preparing formulations in a variety of forms are also described in Anthony L.L. Hunting (ed.), "A Formulary of Cosmetic Preparations (Vol. 2) -- Creams, Lotions and Milks," Micelle Press (England, N.J. 1993). See, for example, Chapter 7, pp. 5-14 (oils and gels); Chapter 8, pp. 15-98 (bases and emulsions); Chapter 9, pp. 101-120 ("all-purpose products"); Chapter 10, pp. 121-184 (cleansing masks, creams, lotions); Chapter 11, pp. 185-208 (foundation, vanishing and day creams); Chapter 12, pp. 209-254 (emollients); Chapter 13, pp. 297-324 (facial treatment products); Chapter 14, pp. 325-380 (hand products); Chapter 15, pp. 381-460 (body and skin creams and lotions); and Chapter 16, pp. 461-484 (baby products); the contents of which are incorporated herein by reference.

The formulations of the invention are most preferably prepared such that the formulation (as occurring with any accompanying components) is substantially invisible upon application to the skin. This is particularly true in the case of many cosmetic formulations that are applied to the face or other exposed parts of the body, although it is also generally desirable that the formulation not be visible even if applied to non-exposed portions of the body. It will be recognized that in some cases, particularly with colored facial skin care products such as blushes, blemish covers, lipsticks and the like, the formulation will be designed to be visible on the skin; in such cases, it is desirable that the polyamine anti-irritant component itself be "invisible," that is, that it not adversely change the appearance of the overall formulation as applied to the skin.

In another embodiment of the invention, the present anti-irritant species can be formulated in a form for topical oral administration to treat pain or irritation in

the mouth, throat or other portions of the upper gastrointestinal tract such as that due to sore throats, canker sores, gum irritation or inflammation or the like, including such irritation as may be exacerbated by spicy or acidic foods as, for example, in the case of ulcers or heartburn. Suitable forms for such oral administration include liquids (e.g. mouthwash or gargle solutions), lozenges, tablets, pills and capsules. As with other topical forms described herein, the components used in such oral formulations should be chosen to be non-toxic. Methods for preparing oral formulations suitable for use in the present invention are well known in the art.

Similarly, formulations suitable for rectal, vaginal, nasal, pulmonary, respiratory, laryngopharyngeal, otic and ocular uses are contemplated and may be readily prepared.

Clinical Results

The anti-irritant efficacy of the formulations of the present invention was tested and confirmed in numerous clinical trials, the results of which are described in the examples below. While these examples further illustrate various aspects and preferred embodiments of the invention as described herein, they are examples only, and should not be considered as limiting the scope of the invention as set forth in the claims.

Example 1

Clinical Studies of Anti-Irritation Activity

The objective of the clinical trials was to determine whether and to what extent the compounds of the present invention reduced or prevented skin irritation caused by lactic acid, an α-hydroxy carboxylic acid known for its skin irritating potential. The trials were conducted in a double blind, randomized, vehicle-

controlled manner. Various formulations of the invention were tested in over 250 people.

1. Protocol

The subjects were women who had been screened and shown to exhibit normal to above normal susceptibility to irritation by the tested irritant. Tests were conducted in multiple panels of from 7 to 12 subjects each. Subjects were instructed not to wear any makeup or facial lotions to the clinic the day of testing. The subjects were instructed to wash their face with Ivory bar soap in the clinic prior to application of test solutions.

Lactic acid skin-irritant compositions were formulated in an appropriate vehicle prior to application to the skin of the subjects. In the majority of the tests, the irritant composition was 7.5% lactic acid dissolved in a 10% ethanol-in-water solution. Other skin tests, such as those using capsaicin or benzoyl peroxide, are also suitable for evaluating the anti-irritant activity of the compounds.

Test anti-irritant formulations were prepared by combining measured amounts of polyamine anti-irritants (Sigma or Aldrich) of the present invention (concentration 250 mM) in the lactic acid irritant composition. The test formulation was applied to a defined portion of the subject's skin, typically the face. Controls were performed by applying a corresponding formulation without any added polyamine anti-irritant to a contralateral portion of the subject's skin.

All test solutions (including controls) were applied in a double blind, randomized fashion using the prepared solutions as previously placed in coded vials designated for use on either the right or left side of the face (or other test area). Solutions were typically applied using a cotton swab (six strokes) or sponge applicator to the face and cheek area extending from the midline of the nose over to

the center of the cheek and from the cheek bone down to the jaw line. Application was made first to the right side and then to the left.

Sensory assessment scores were recorded for each treated side of the subject's skin every minute for 10 minutes or until three consecutive scores of "zero" irritation were obtained. The following scaled scores were used for sensory assessment:

Score	Description of Irritation
0	**NO irritation**
1	**SLIGHT irritation --** (Barely perceptible stinging, burning or itching)
2	**MILD irritation --** (Definite stinging, burning or itching)
3	**MODERATE irritation --** (Distinctly uncomfortable stinging, burning or itching; constantly aware of irritation)
4	**SEVERE irritation --** (Continuous stinging, burning or itching, and intensely uncomfortable; would interfere with daily routine)

Symptom scores were cumulated, separately for the anti-irritant-treated and control-treated areas, for each individual and also for the panel as a whole. Individuals not reporting a cumulative score of at least "7" on at least one treatment area were excluded (in a blinded fashion) from further analysis in order to ascertain anti-irritant efficacy with respect to the more severely-susceptible test subjects.

From a practical standpoint, scores of "0" and "1" on the above scale would be considered highly desirable for a commercial product because such a response would likely not result in a consumer ceasing to use a product. Some consumers, in fact, might view the "barely perceptible" sensations represented by a score of 1 to be an indication that a facial treatment skin care product (especially an exfoliant) was working as advertised. By contrast, irritation scores of "2", "3" and "4" would likely often result in a consumer never purchasing the product again.

In those subjects and skin samples where an irritation was sensed, the irritation commonly involved a spectrum of burn-sting-itch reactions over time. For example, a subject might at first experience a sting, but moments later might experience an itch with no sting. Subjects experiencing higher levels of irritation (e.g. scores of "3" or "4") occasionally exhibited erythema (visually observable inflammation) in addition to sensory irritation effects.

2. Results

Clinical tests, performed as generally described above, demonstrated that the polyamine anti-irritant compounds of the invention have significant and reproducible anti-irritant effects, particularly if administered simultaneously with an irritant compound.

A representative set of test results, performed using acid anti-irritant concentrations of 250 mM, is set forth in Tables 1 and 2 below. Table 1 reports representative test results using various straight-chain, branched-chain and heterocyclic polyamines. Table 2 lists representative test results for amino acid compounds of the lysine, arginine, histidine and ornithine families, including various derivatized amino acids.

Where multiple panels were studied (n > 1), the percent inhibition is reported as the average of observed values and represents the cumulative irritation inhibition value.

Anti-Irritant Data

TABLE 1

Polyamine Type	Compound	% inhibition (n)*
Straight-Chain	Spermine•4HCl Spermidine Putrescine•2HCl	52 42 50 (n=2)
Branched-Chain	Protamine (Gr. IV)	37 (n=2)
Heterocyclic	HEPES Imidazole Piperazine	71 (n=2) 50 61

TABLE 2

Amino acid Family	Compound	% inhibition (n)*
Lysine	L-Lysine•HCl D-Lysine•HCl L-Lysine methyl ester•2HCl L-Lysine ethyl ester•2HCl N-α-Acetyl-L-Lysine N-α-Acetyl-L-Lysine methyl ester•HCl N-ϵ-Acetyl-L-Lysine L-Lysinamide•2HCl Hydroxy-Lysine	61 (n=2) 51 (n=2) 57 52 63 (n=2) 40 46 (n=2) 39 60

Amino acid Family	Compound	% inhibition (n)*
Arginine	L-Arginine	39 (n=3)
	D-Arginine	38
	L-Arginine ethyl ester•2HCl	69 (n=2)
	Homo-Arginine	39
Histidine	L-Histidine	61 (n=2)
	D-Histidine	34
	L-Histidine methyl ester•2HCl	46 (n=2)
	L-Histidine benzyl ester•Di-p-toluenesulfonamide	56
	Carnosine	36 (n=2)
Ornithine	L-Ornithine•HCl	43 (n=2)
	Citrulline	35

* Unless stated otherwise, n=1. Note that n = number of panels, not subjects.

FIGURES 1 through 8 show more detailed experimental data for two panel tests conducted using L-arginine (FIGS. 1-4) and L-lysine (FIGS. 5-8) (250 mM each) as anti-irritant components of the subject formulations. FIGS. 1 and 5 show the time course of irritation responses for both anti-irritant-treated and non-treated (control) skin portions for the panels. FIGS. 2 and 6 show the cumulative irritation over time for the same panels, while FIGS. 3-4 and 7-8 show cumulative irritation suppression and treated/untreated irritation responses on a subject-by-subject basis. While individual responses vary somewhat, the overall efficacy of the subject formulations is evident.

As noted above, the anti-irritant compounds of the invention are preferably chosen from compounds that are not themselves irritating to the user. Ethylenediamine, a small straight-chain polyamine, is an example of a compound reported to have irritant properties (Merck Index, Eleventh edition). Preliminary

clinical tests of ethylenediamine using the protocol described above yielded variable results and suggested that the compound has relatively low anti-irritant properties (<20% inhibition) for some subjects and in fact may increase irritation somewhat (less than 20%) in some users.

Example 2

Dose-Response Study

A study of anti-irritant activity using different concentrations of L-arginine was conducted in order to assess the dose-response behavior of the present formulations. The lactic acid protocol described above was used. Irritation inhibition data are set forth in the following table and indicate anti-irritant activity at lower concentration (125 mM).

L-Arginine Concentration (mM)	Percent Inhibition
125	21%
250	53%

The foregoing examples are not intended to limit the scope of the present invention, which is set forth in the following claims. In particular, various equivalents and substitutions will be recognized by those skilled in the art in view of the foregoing disclosure, and these are contemplated to be within the scope of the invention.

What is claimed is:

1. A composition for topical application to an animal subject comprising a topical vehicle;
an irritant ingredient contained in an amount capable of inducing skin irritation in said subject; and
an anti-irritant component comprising an anti-irritant amount of one or more aqueous-soluble polyamines having a plurality of protonated amino moieties.

2. The composition of claim 1 wherein said aqueous-soluble polyamine is selected from the group consisting of spermine, spermidine, putresine, protamine, imidazole, piperazine, and HEPES.

3. The composition of claim 1 wherein said aqueous-soluble polyamine is an amino acid having a positively-charged nitrogen-containing side chain.

4. The composition of claim 3 wherein said amino acid is selected from the group consisting of arginine, lysine, histidine, and ornithine.

5. A composition for topical application to an animal subject comprising a topical vehicle;
an irritant ingredient contained in an amount capable of inducing skin irritation in said subject; and
an anti-irritant component comprising an anti-irritant amount of one or more aqueous-soluble amino acids having a positively-charged nitrogen-containing side chain.

6. The composition of claim 5 wherein said aqueous-soluble amino acid is selected from the group consisting of arginine, lysine, histidine, and ornithine.

7. The composition of claim 5 wherein said anti-irritant component comprises at least one derivatized amino acid having a positively-charged nitrogen-containing side chain, said derivatized amino acid consisting of an amino acid and a substituent selected from N-α-terminal substituents of the form RCO- and R-, and C-terminal substituents of the form $-NH_2$, $-NHNH_2$, -NHR, $-NR_2$ and -OR (where each R is independently selected from unbranched and branched, unsubstituted and substituted lower alkyl, alkenyl, and alkynyl groups of from 1 to about 10 carbons, aryl, alkaryl, aralkyl and cycloalkyl groups of from about 3 to about 20 carbons, and, in the case of $-NR_2$, from cyclized groups forming (in attachment with the nitrogen atom) a 5-8 membered heterocyclic ring optionally containing an oxygen or nitrogen as a further ring heteroatom).

8. The composition of claim 7 wherein said derivatized amino acid is selected from derivatives of arginine, lysine, histidine, and ornithine.

9. The composition of claim 7 wherein said RCO- substituent is an acetyl substituent.

10. The composition of claim 7 wherein said derivatized amino acid is an ester form of the amino acid.

11. The composition of claim 1 or 5 wherein said anti-irritant component is present at a concentration of from about 10 mM to about 3000 mM.

12. The composition of claim 1 or 5 wherein said anti-irritant component is present at a concentration of from about 50 mM to about 2000 mM.

13. The composition of claim 1 or 5 wherein said anti-irritant component is present at a concentration of from about 100 mM to about 1000 mM.

14. The composition of claim 1 or 5 comprising an amount of said anti-irritant component capable of inhibiting mean cumulative skin irritation attributable to said irritant ingredient in a susceptible human population by at least about 20%.

15. The composition of claim 14 wherein said inhibition of skin irritation represents an average reduction in one or more of sting, burn and itch in a susceptible human population upon topical application of said composition, as compared to the level of irritation induced in said population upon topical application of a control formulation containing said irritant ingredient in a vehicle without said anti-irritant component.

16. The composition of claim 1 or 5 comprising an amount of said anti-irritant component capable of inhibiting by at least about 40% the cumulative skin irritation attributable to said irritant ingredient in at least 10% of the susceptible human population.

17. The composition of claim 16 wherein said inhibition of skin irritation represents an average reduction in one or more of sting, burn and itch in a susceptible human population upon topical application of said composition, as compared to the level of irritation induced in said population upon topical

application of a control formulation containing said irritant ingredient in a vehicle without said anti-irritant component.

18. The composition of claim 1 or 5 wherein said composition is a cosmetic product.

19. The composition of claim 18 wherein said composition comprises a skin exfoliant, skin peel or skin cell renewal agent.

20. The composition of claim 18 wherein said irritant ingredient is selected from the group consisting of carboxylic acids, keto acids, α-hydroxy acids, β-hydroxy acids, retinoids, peroxides, and organic alcohols.

21. The composition of claim 20 wherein said irritant ingredient comprises lactic acid or a salt thereof.

22. The composition of claim 20 wherein said irritant ingredient comprises glycolic acid or a salt thereof.

23. The composition of claim 20 wherein said irritant ingredient comprises salicylic acid or a salt thereof.

24. The composition of claim 20 wherein said irritant ingredient comprises a combination of lactic acid and salicylic acid, or salts thereof.

25. The composition of claim 20 wherein said irritant ingredient comprises capryloyl salicylic acid or a salt thereof.

26. The composition of claim 20 wherein said irritant ingredient comprises citric acid or a salt thereof.

27. The composition of claim 20 wherein said irritant ingredient is a retinoid selected from tretinoin, retinol, retinal and derivatives thereof.

28. The composition of claim 20 wherein said irritant ingredient comprises benzoyl peroxide.

29. The composition of claim 20 wherein said irritant ingredient comprises acetic acid or a salt thereof.

30. The composition of claim 20 wherein said irritant ingredient comprises one or more of the group consisting of l-pyrrolidone-5-carboxylic acid, capryloyl salicylic acid, α-hydroxy decanoic acid, α-hydroxy octanoic acid, gluconolactone, methoxypropyl gluconamide, oxalic acid, malic acid, tartaric acid, mandelic acid, benzylic acid, gluconic acid, pyruvic acid and phenol.

31. The composition of claim 20 wherein said irritant ingredient comprises trichloroacetic acid or a salt thereof.

32. The composition of claim 20 wherein the pH of the composition is in the range of 1 to 6.

33. The composition of claim 20 wherein the pH of the composition is in the range of 2 to 4.

34. The composition of claim 20 having a concentration of said irritant ingredient of from about 0.01% to about 50%.

35. The composition of claim 20 having a concentration of said irritant ingredient of from about 0.5% to about 20%.

36. The composition of claim 1 or 5 wherein said composition is an antiperspirant or deodorant product.

37. The composition of claim 1 or 5 wherein said composition is a sunscreen, tanning or sunburn treatment product.

38. The composition of claim 1 or 5 wherein said composition is an insect repellant product.

39. The composition of claim 18 wherein said composition is a shaving or hair removal product selected from the group consisting of depilatory, bracer, cream, foam, gel and aftershave products.

40. The composition of claim 18 wherein said composition is a hair care or hair treatment product.

41. The composition of claim 40 wherein said composition is selected from the group consisting of shampoo, conditioner, colorant, dye, bleach, permanent wave and hair straightener products.

42. The composition of claim 18 wherein said composition is selected from the group consisting of cleansers, astringents, toners, rinses, serums and masks.

43. The composition of claim 18 wherein said composition is a facial cosmetic product.

44. The composition of claim 18 wherein said composition is selected from the group consisting of creams, lotions and moisturizers.

45. The composition of claim 1 or 5 wherein said composition is selected from the group consisting of soaps and detergents.

46. The composition of claim 1 or 5 wherein said composition is a topical drug product.

47. The composition of claim 46 wherein said irritant ingredient is capsaicin.

48. The composition of claim 46 wherein said composition is selected from the group consisting of antibiotic, analgesic, contraceptive, anti-acne and anti-dandruff products.

49. The composition of claim 48 wherein said irritant ingredient is benzoyl peroxide.

50. The composition of claim 1 or 5 wherein said composition is formulated as a rectal or vaginal suppository, foam, cream, gel, ointment, douche or enema.

51. The composition of claim 1 or 5 wherein said composition is formulated for administration to the mouth, throat or lip.

52. The composition of claim 51 formulated as a lozenge, mouthwash or gargle.

53. The composition of claim 1 or 5 formulated as a liquid, gel, cream, emulsion, suspension or stick.

54. The composition of claim 1 or 5 formulated with a physical applicator.

55. The composition of claim 54 wherein said physical applicator is selected from the group consisting of cloths, tissues, swabs, bandages and wet wipes.

56. The composition of claim 1 or 5 wherein said composition is formulated for administration to the respiratory system.

57. The composition of claim 56 formulated as a mist or spray.

58. The composition of claim 1 or 5 wherein said composition is formulated for otic administration.103

59. The composition of claim 1 or 5 wherein said composition is formulated for administration to the reproductive system.

60. The composition of claim 1 or 5 wherein said composition is formulated for ocular administration.

61. The composition of claim 1 or 5 wherein said composition is formulated for administration to the gastrointestinal system.

62. The composition of claim 1 or 5 further comprising at least one second anti-irritant agent.

63. The composition of claim 62 wherein the total amount of said anti-irritant component and said second agent is capable of inhibiting mean cumulative skin irritation attributable to said irritant ingredient in a susceptible human population by at least about 20%.

64. The composition of claim 62 wherein the total amount of said anti-irritant component and said second agent is capable of inhibiting by at least about 40% the cumulative skin irritation attributable to said irritant ingredient in at least 10% of the susceptible human population.

65. The composition of claim 62 wherein said second agent is selected from the group consisting of potassium channel mediating, regulating or blocking agents, calcium channel blocking or regulatory agents, sodium channel blocking agents, steroids, non-steroidal anti-inflammatory agents, aloe vera, chamomile, α-bisabolol, Cola nitida extract, green tea extract, tea tree oil, licorice extract, allantoin, urea, caffeine and other xanthines, and glycyrrhizic acid and its derivatives.

66. A composition for inhibiting skin irritation in an animal subject containing an anti-irritant component comprising an anti-irritant amount of one or more aqueous-soluble polyamines having a plurality of protonated amino moieties.

67. The composition of claim 66 wherein said aqueous-soluble polyamine is selected from the group consisting of spermine, spermidine, putrescine, protamine, imidazole, piperazine, and HEPES.

68. The composition of claim 66 wherein said aqueous-soluble polyamine is an amino acid having a positively-charged nitrogen-containing side chain.

69. The composition of claim 68 wherein said amino acid is selected from the group consisting of arginine, lysine, histidine, and ornithine.

70. A composition for inhibiting skin irritation in an animal subject containing an anti-irritant component comprising an anti-irritant amount of one or more aqueous-soluble amino acids having a positively-charged nitrogen-containing side chain.

71. The composition of claim 70 wherein said aqueous-soluble amino acid is selected from the group consisting of arginine, lysine, histidine, and ornithine.

72. The composition of claim 70 wherein said anti-irritant component comprises at least one derivatized amino acid having a positively-charged nitrogen-containing side chain, said derivatized amino acid consisting of an amino acid and a substituent selected from N-α-terminal substituents of the form RCO- and R-, and C-terminal substituents of the form $-NH_2$, $-NHNH_2$, -NHR, $-NR_2$ and -OR (where each R is independently selected from unbranched and branched, unsubstituted and substituted lower alkyl, alkenyl, and alkynyl groups of from 1 to about 10 carbons, aryl, alkaryl, aralkyl and cycloalkyl groups of from about 3 to about 20 carbons, and, in the case of $-NR_2$, from cyclized groups forming (in attachment with the nitrogen atom) a 5-8 membered saturated heterocyclic ring optionally containing an oxygen or nitrogen as a further ring heteroatom).

73. The composition of claim 72 wherein said derivatized amino acid is selected from derivatives of arginine, lysine, histidine, and ornithine.

74. The composition of claim 66 or 70 comprising said anti-irritant component in a concentration of from about 10 mM to about 3000 mM.

75. The composition of claim 66 or 70 comprising said anti-irritant component in a concentration of from about 50 mM to about 2000 mM.

76. The composition of claim 66 or 70 comprising said anti-irritant component in a concentration of from about 100 mM to about 1000 mM.

77. The composition of claim 66 or 70 wherein said inhibition of skin irritation represents a reduction in skin irritation attributable to a pre-existing skin disease or skin irritation condition.

78. The composition of claim 77 wherein said skin irritation is attributable to atopic dermatitis, non-atopic dermatitis, asthma, rhinitis, conjunctivitis, eczema, psoriasis or infectious disease.

79. The composition of claim 66 or 70 wherein said skin irritation is ocular irritation.

80. The composition of claim 66 or 70 wherein said skin irritation is respiratory system irritation.

81. The composition of claim 66 or 70 wherein said skin irritation is gastrointestinal irritation.

82. The composition of claim 66 or 70 wherein said skin irritation is reproductive system irritation.

83. The composition of claim 66 or 70 wherein said skin irritation is irritation of a mucous membrane.

84. The composition of claim 66 or 70 wherein said skin irritation is irritation of epidermal skin.

85. The composition of claim 66 or 70 wherein said skin irritation is irritation of dermal skin.

86. The composition of claim 77 wherein said skin irritation is attributable to environmental exposure to one or more of sunlight, low humidity, wind, cold temperature, or hot and humid conditions.

87. The composition of claim 77 wherein said skin irritation is attributable to exposure to an irritating chemical agent.

88. The composition of claim 87 wherein said irritating chemical agent exposure is attributable to application of a topical product.

89. The composition of claim 88 wherein said product is selected from the group consisting of antiperspirant, deodorant, sunscreen, tanning, sunburn treatment, insect repellant, exfoliant, skin peel, skin cell renewal, fragrance, shaving or hair removal, hair care or hair treatment, eye care or contact lens solutions, cleanser, astringent, toner, rinse, serum, masks, facial cosmetic, cream, lotion, moisturizer, soap, detergent, and topical drug products.

90. The composition of claim 88 wherein said composition is packaged with instructions directing administration of said composition before, with or following administration of said topical product.

91. The composition of claim 87 wherein said irritating chemical agent exposure is attributable to insect sting or bite, or to plant exposure.

92. The composition of claim 76 wherein said skin irritation is attributable to one or more of shaving, skin cleansing or bathing, sweating, and physical skin trauma.

93. The composition of claim 66 or 70 wherein said skin irritation is attributable to dry skin.

94. The composition of claim 66 or 70 comprising an amount of said anti-irritant component capable of inhibiting said skin irritation in subjects experiencing the same by an average of at least about 20%.

95. The composition of claim 66 or 70 comprising an amount of said anti-irritant component capable of inhibiting said skin irritation by at least about 40% in at least 10% of the subjects experiencing the same.

96. The composition of claim 66 or 70 wherein said composition is formulated as a rectal or vaginal suppository, cream, foam, gel, ointment, enema or douche.

97. The composition of claim 66 or 70 wherein said composition is formulated for administration to the mouth, throat or lip.

98. The composition of claim 97 formulated as a lozenge, mouthwash or gargle.

99. The composition of claim 66 or 70 formulated as a liquid, gel, cream, emulsion, suspension or stick.

100. The composition of claim 66 or 70 formulated with a physical applicator.

101. The composition of claim 66 or 70 wherein said composition is formulated for administration to the respiratory system.

102. The composition of claim 101 formulated as a mist or spray.

103. The composition of claim 66 or 70 wherein said composition is formulated for otic administration.

104. The composition of claim 66 or 70 wherein said composition is formulated for administration to the gastrointestinal system.

105. The composition of claim 66 or 70 wherein said composition is formulated for ocular administration.

106. The composition of claim 66 or 70 wherein said composition is formulated for administration to the reproductive system.

107. The composition of claim 66 or 70 further comprising at least one second anti-irritant agent.

108. The composition of claim 107 wherein said second agent is selected from the group consisting of potassium channel mediating, regulating or blocking agents, calcium channel blocking or regulatory agents, sodium channel blocking agents, steroids, non-steroidal anti-inflammatory agents, aloe vera, chamomile, α-bisabolol, Cola nitida extract, green tea extract, tea tree oil, licorice extract, allantoin, urea, caffeine and other xanthines, and glycyrrhizic acid and its derivatives.

109. A method for inhibiting skin irritation associated with an irritant ingredient contained in an applied topical formulation, comprising topically administering to an animal subject the composition of claim 1 or 5.

110. A method for inhibiting skin irritation in a animal subject comprising topically administering to the subject the composition of claim 66 or 70.

111. The method of claim 110 wherein said composition is administered within about three hours prior to application to the subject of a second topical formulation containing an irritant ingredient.

112. The method of claim 110 wherein said composition is administered substantially simultaneously with application to the subject of a second topical formulation containing an irritant ingredient.

113. The method of claim 110 wherein said composition is administered to inhibit skin irritation attributable to a pre-existing animal skin disease or skin irritation condition.

114. The method of claim 110 wherein said skin irritation is ocular irritation.

115. The method of claim 110 wherein said skin irritation is respiratory system irritation.

116. The method of claim 110 wherein said skin irritation is gastrointestinal system irritation.

117. The method of claim 110 wherein said skin irritation is reproductive system irritation.

118. The method of claim 110 wherein said skin irritation is irritation of a mucuous membrane.

119. The method of claim 110 wherein said skin irritation is irritation of epidermal skin.

120. The method of claim 110 wherein said skin irritation is irritation of dermal skin.

121. The method of claim 113 wherein said skin irritation is attributable to environmental exposure to one or more of sunlight, low humidity, wind, cold temperature, or hot and humid conditions.

122. The method of claim 113 wherein said skin irritation is attributable to exposure to an irritating chemical agent.

123. The method of claim 113 wherein said skin irritation is attributable to one or more of shaving, skin cleansing or bathing, and physical skin trauma.

FIG. 1

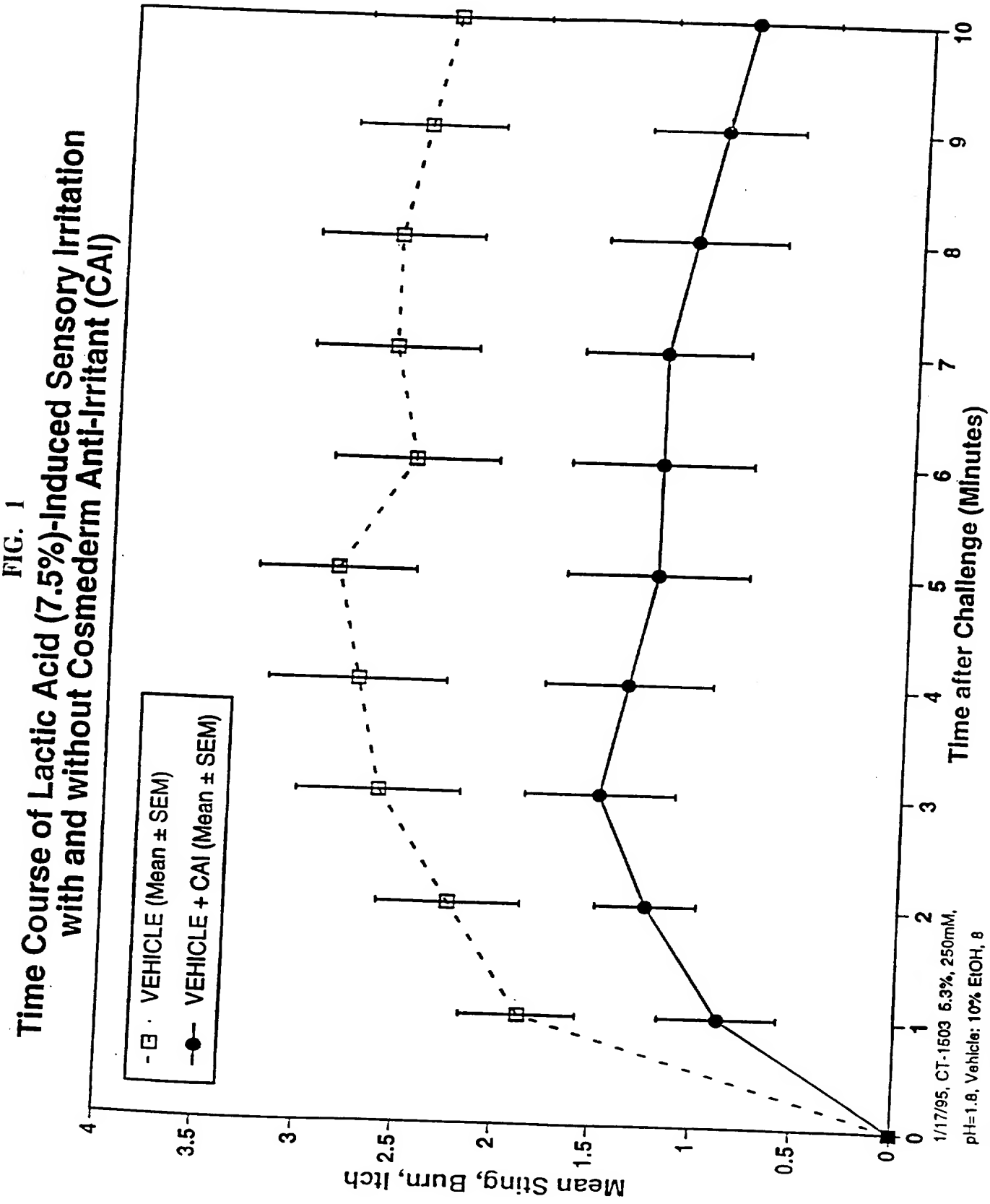

Time Course of Lactic Acid (7.5%)-Induced Sensory Irritation
with and without Cosmederm Anti-Irritant (CAI)
VEHICLE (Mean ± SEM)
VEHICLE + CAI (Mean ± SEM)
Mean Sting, Burn, Itch
Time after Challenge (Minutes)
0
0.5
1
1.5
2
2.5
3
3.5
4
0
1
2
3
4
5
6
7
8
9
10
1/17/95, CT-1503 5.3%, 250mM,
pH=1.8, Vehicle: 10% EtOH, 8
Subjects, Mixed at time zero.

FIG. 2

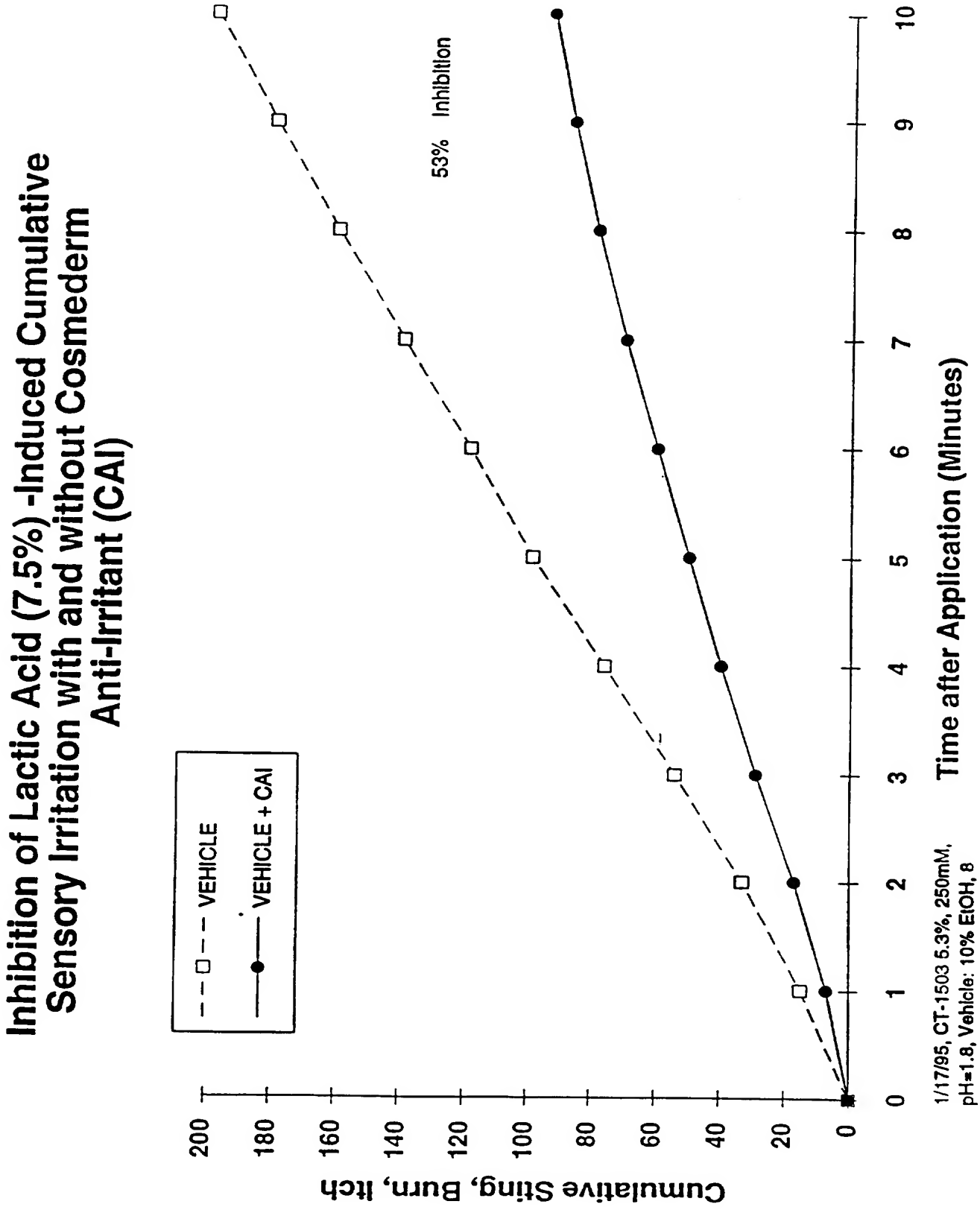

Inhibition of Lactic Acid (7.5%) -Induced Cumulative Sensory Irritation with and without Cosmederm Anti-Irritant (CAI)
VEHICLE
VEHICLE + CAI
53% Inhibition
Cumulative Sting, Burn, Itch
Time after Application (Minutes)
0
20
40
60
80
100
120
140
160
180
200
0
1
2
3
4
5
6
7
8
9
10
1/17/95, CT-1503 5.3%, 250mM, pH=1.8, Vehicle: 10% EtOH, 8 Subjects, Mixed at time zero.

FIG. 3

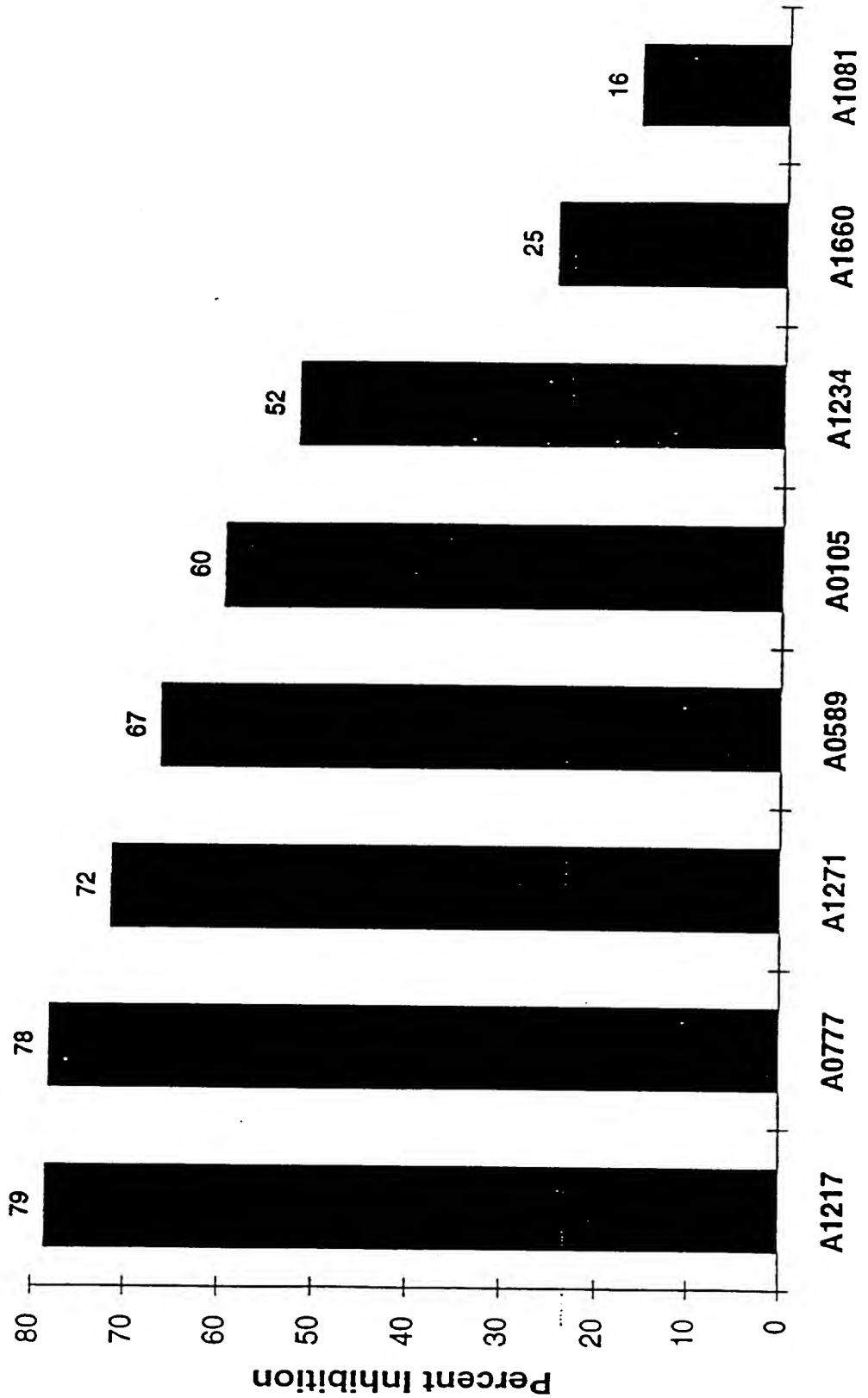

Suppression of Individual Subject's Sensory Irritation by Lactic Acid (7.5%) with and without Cosmederm Anti-Irritant (CAI)
Percent Inhibition
0
10
20
30
40
50
60
70
80
79
78
72
67
60
52
25
16
A1217
A0777
A1271
A0589
A0105
A1234
A1660
A1081
Subject ID
1/17/95, CT-1503 5.3%, 250mM, pH=1.8, Vehicle: 10% EtOH, 8 Subjects, Mixed at time zero.

FIG. 4

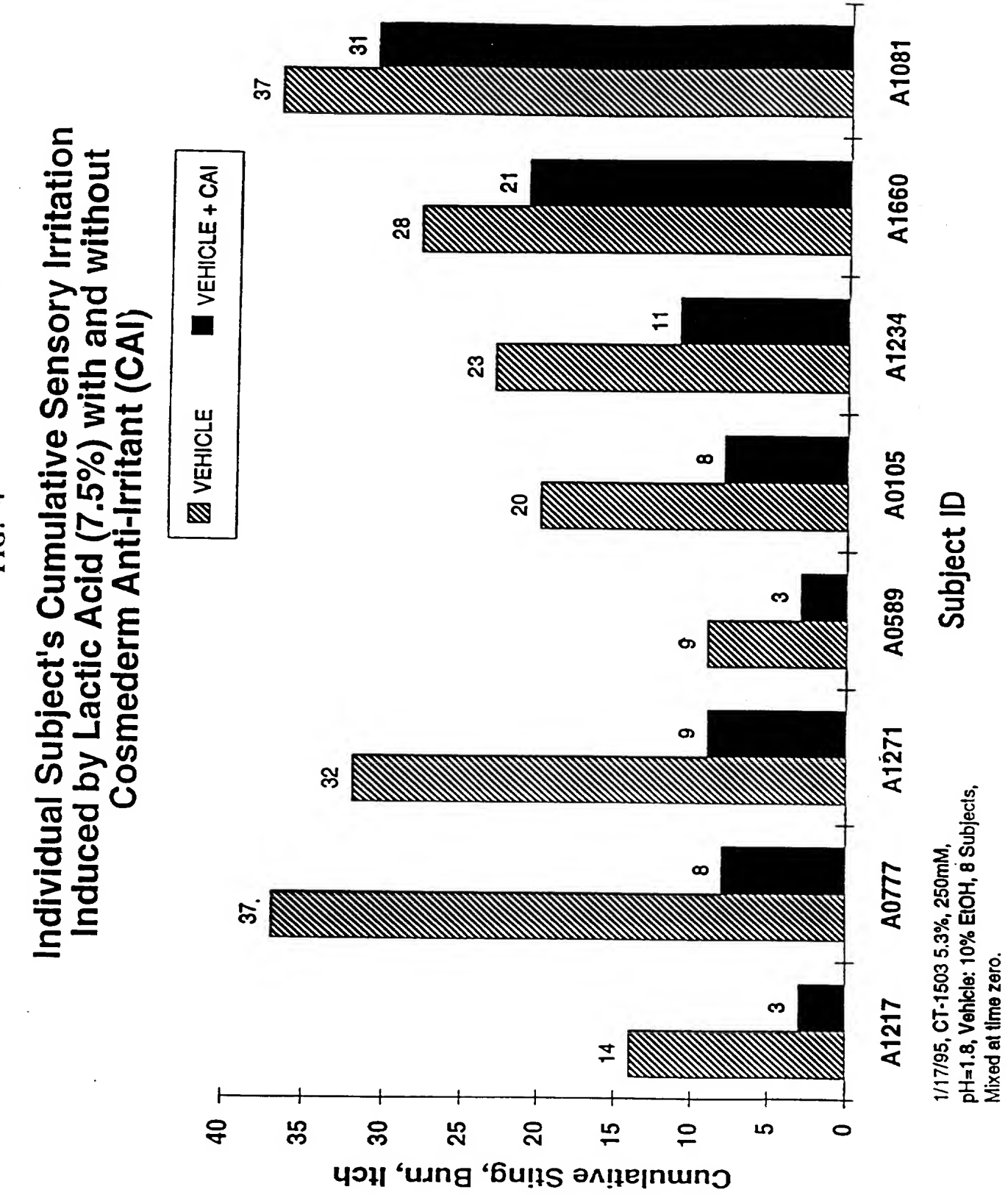

Individual Subject's Cumulative Sensory Irritation Induced by Lactic Acid (7.5%) with and without Cosmederm Anti-Irritant (CAI)
VEHICLE
VEHICLE + CAI
Cumulative Sting, Burn, Itch
0
5
10
15
20
25
30
35
40
14
3
37
8
32
9
9
3
20
8
23
11
28
21
37
31
A1217
A0777
A1271
A0589
A0105
A1234
A1660
A1081
Subject ID
1/17/95, CT-1503 5.3%, 250mM, pH=1.8, Vehicle: 10% EtOH, 8 Subjects, Mixed at time zero.

FIG. 5

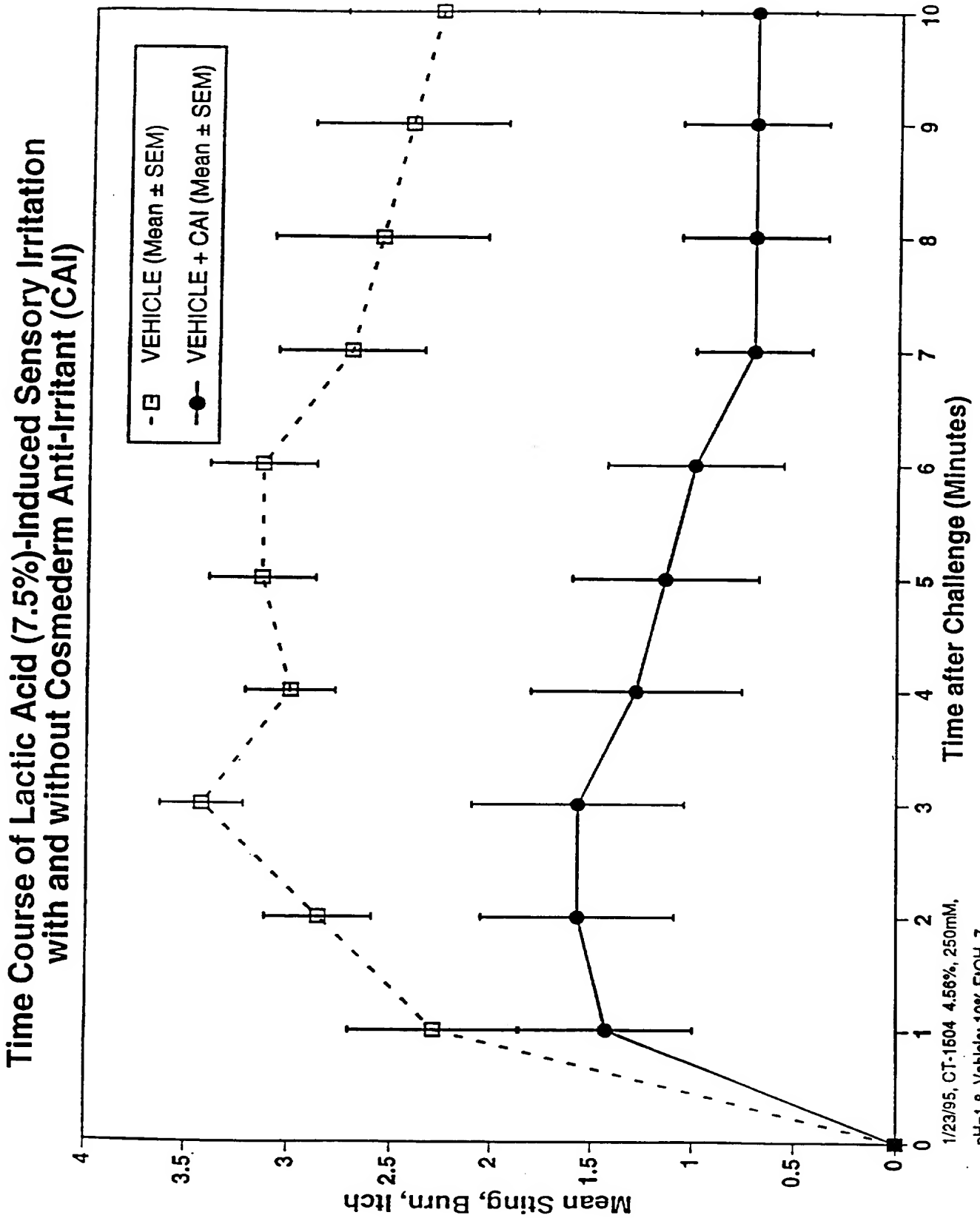

Time Course of Lactic Acid (7.5%)-Induced Sensory Irritation with and without Cosmederm Anti-Irritant (CAI)
VEHICLE (Mean ± SEM)
VEHICLE + CAI (Mean ± SEM)
Mean Sting, Burn, Itch
Time after Challenge (Minutes)
0
0.5
1
1.5
2
2.5
3
3.5
4
0
1
2
3
4
5
6
7
8
9
10
1/23/95, CT-1504 4.56%, 250mM, pH=1.8, Vehicle: 10% EtOH, 7 Subjects, Mixed at time zero.

FIG. 6

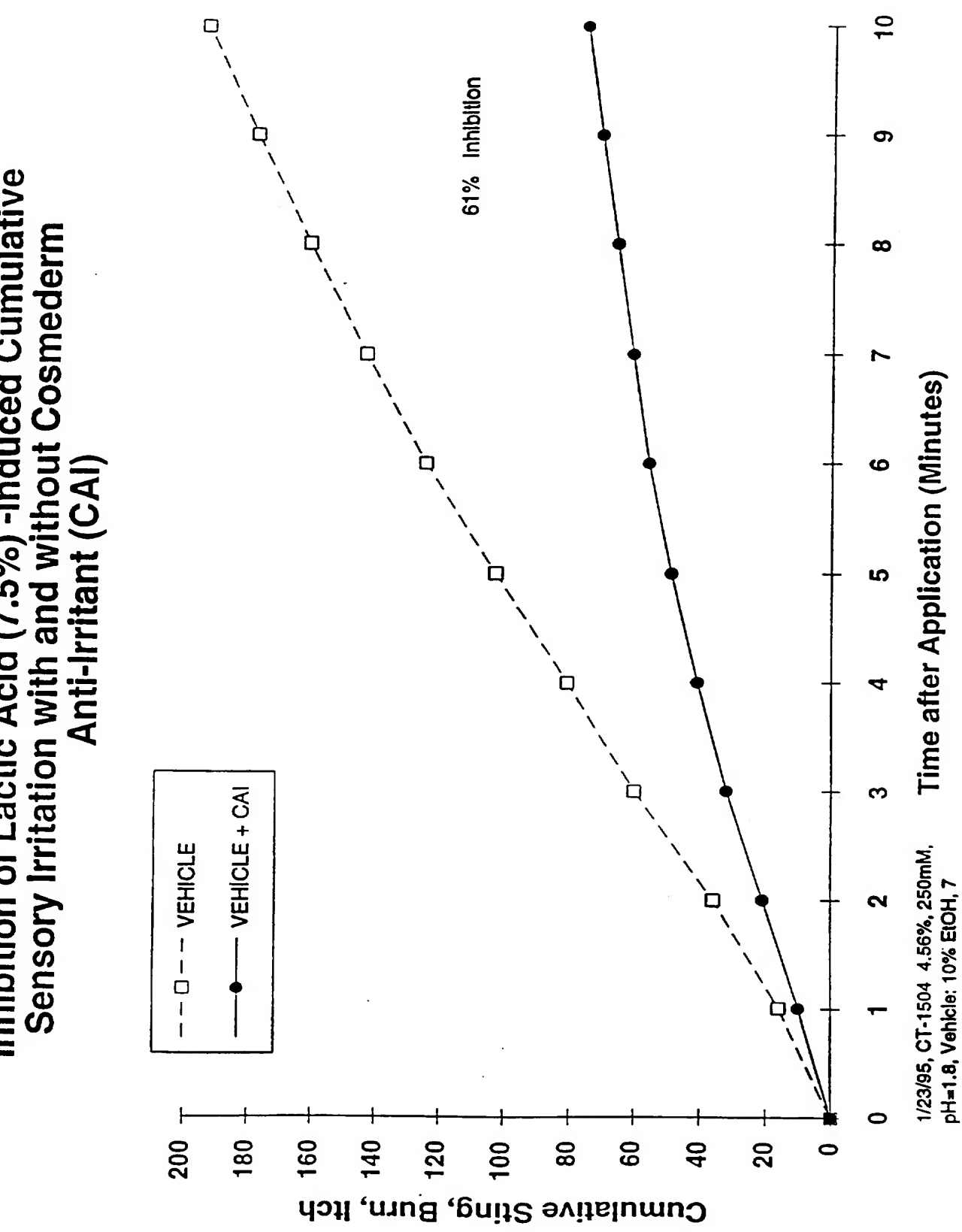

Inhibition of Lactic Acid (7.5%) -Induced Cumulative Sensory Irritation with and without Cosmederm Anti-Irritant (CAI)
VEHICLE
VEHICLE + CAI
61% Inhibition
Cumulative Sting, Burn, Itch
Time after Application (Minutes)
0
20
40
60
80
100
120
140
160
180
200
0
1
2
3
4
5
6
7
8
9
10
1/23/95, CT-1504 4.56%, 250mM, pH=1.8, Vehicle: 10% EtOH, 7 Subjects, Mixed at time zero.

FIG. 7

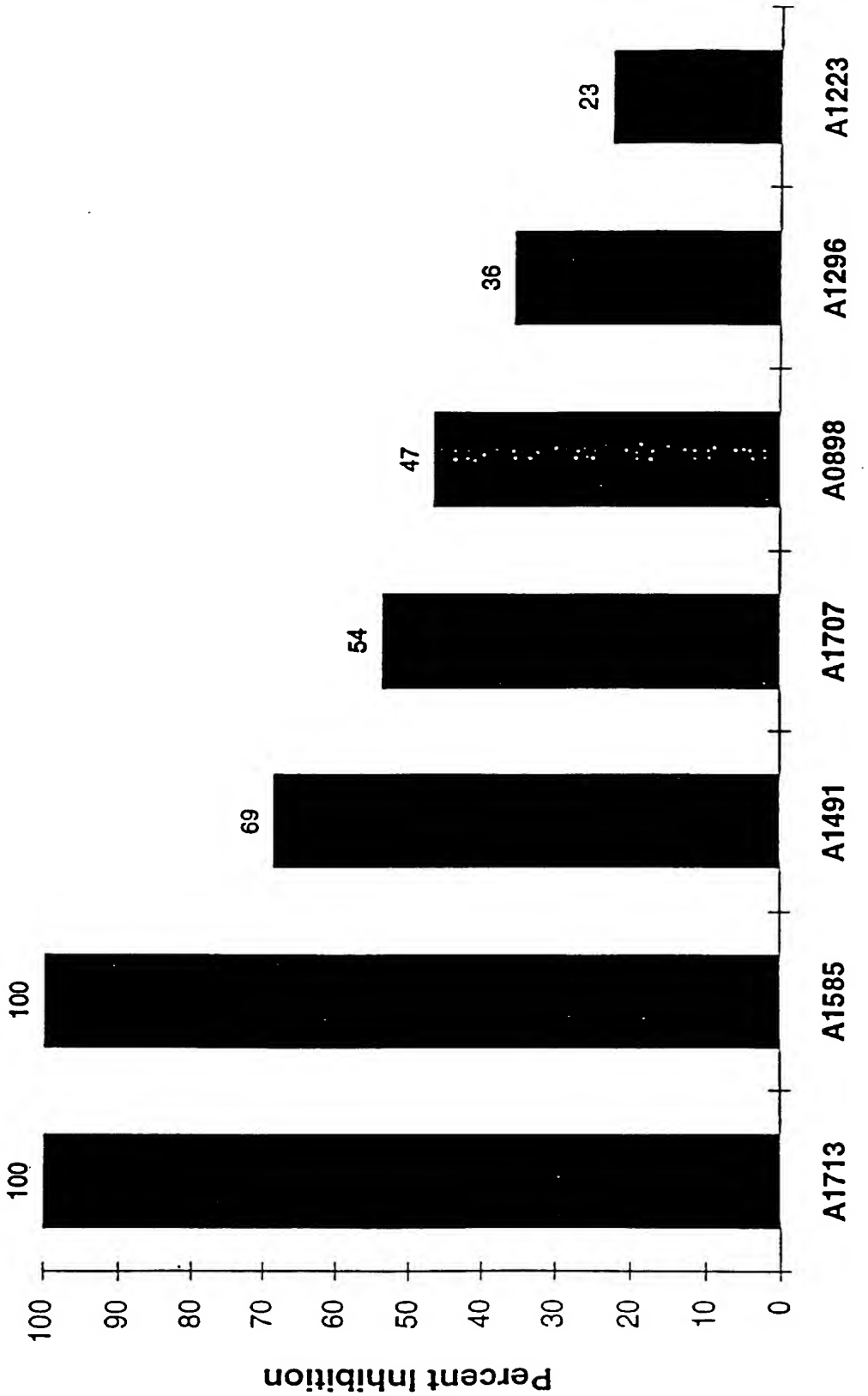
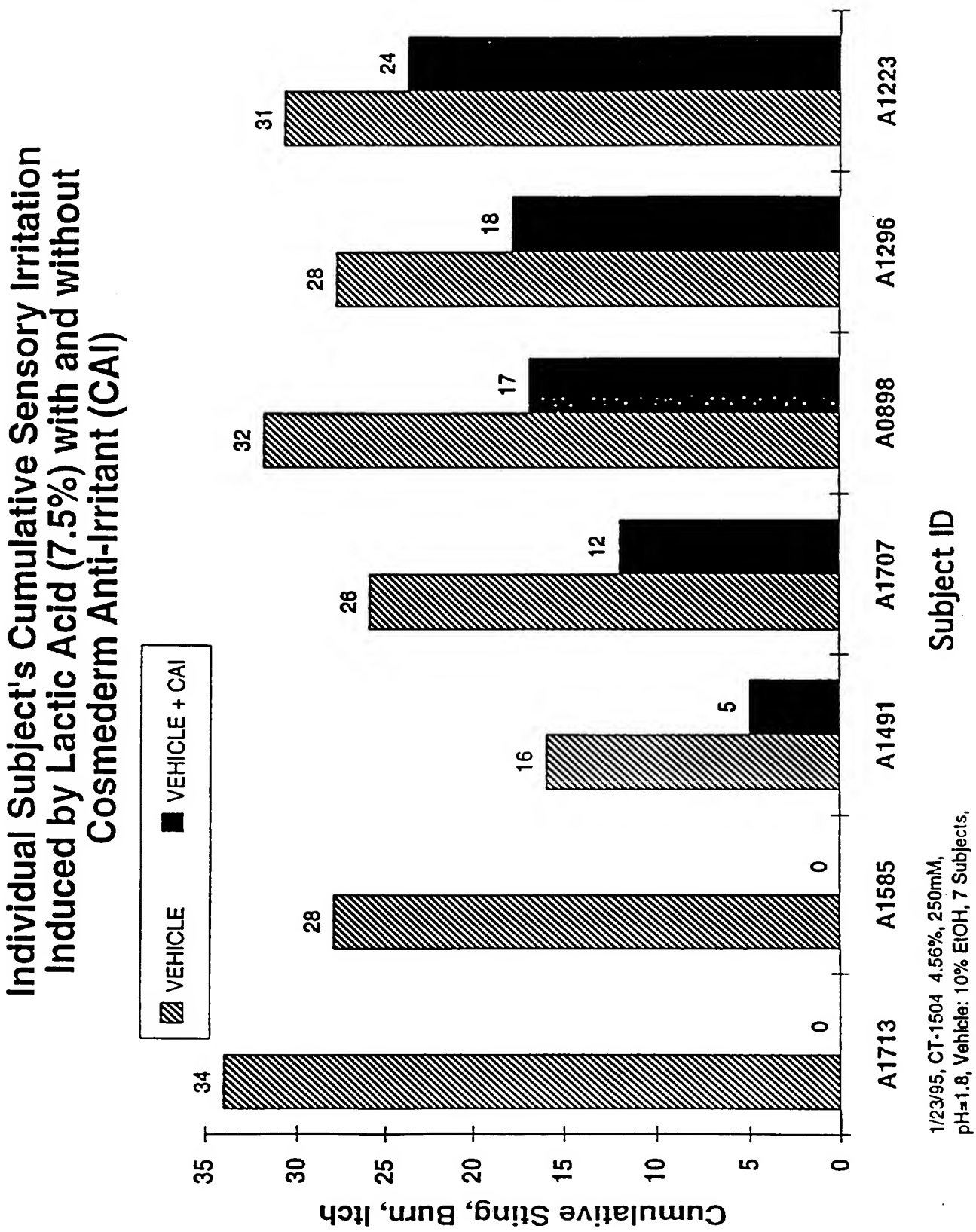

Suppression of Individual Subject's Sensory Irritation by Lactic Acid (7.5%) with and without Cosmederm Anti-Irritant (CAI)
Percent Inhibition
0
10
20
30
40
50
60
70
80
90
100
100
100
69
54
47
36
23
A1713
A1585
A1491
A1707
A0898
A1296
A1223
Subject ID
1/23/95, CT-1504 4.56%, 250mM, pH=1.8, Vehicle: 10% EtOH, 7 Subjects, Mixed at time zero.

FIG. 8


Individual Subject's Cumulative Sensory Irritation Induced by Lactic Acid (7.5%) with and without Cosmederm Anti-Irritant (CAI)
VEHICLE
VEHICLE + CAI
Cumulative Sting, Burn, Itch
0
5
10
15
20
25
30
35
34
0
28
0
16
5
26
12
32
17
28
18
31
24
A1713
A1585
A1491
A1707
A0898
A1296
A1223
Subject ID
1/23/95, CT-1504 4.56%, 250mM, pH=1.8, Vehicle: 10% EtOH, 7 Subjects, Mixed at time zero.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/01289

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/13
US CL : 514/579, 823, 828, 829, 830, 831, 887, 922, 974
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, CASONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MEDLINE ABSTRACT No. 87021350, von den DRIESCH ET AL, Zeitschrigt fur Hautkrankheiten, 61 (16), 15 August 1986. See entire abstract.	1-123
Y	MEDLINE ABSTRACT No. 92027940, VILUKSELA, "Characteristics and modulation of dithranol (anthralin)-induced skin irritation in the mouse ear model", Archives of Dermatological Research, 283 (4), 1991. See entire abstract.	1-123
Y	MEDLINE ABSTRACT No. 92013249, WILHELM et al, "Effect of sodium lauryl sulfate-induced skin irritation on in vivo percutanous penetration of four drugs", Journal of Investigative Dermatology, 97 (5), November 1991. See entire abstract.	1-123

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 28 MAY 1996	Date of mailing of the international search report 06 JUN 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer KEITH MACMILLAN Telephone No. (703) -308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/01289

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MEDLINE ABSTRACT No. 88153675, PIACENTINI et al, "Free and protein-conjugated polyamines in mouse epidermal cells. Effect of high calcium and retinoic acid", Journal of Biological Chemistry, 263 (8), 15 March 1988. See entire abstract.	1-123
Y	MEDLINE ABSTRACT No. 90268590, SASAKI et al, "Enhancing effect of pyrrolidone derivatives on transdermal penetration of phenolsulfonphthalein and indomethacin from aqueous vehicle", Chemical and Pharmaceutical Bulleton, 38 (3), March 1990. See entire abstract.	1-123